Amendments to the Specification

Please amend the paragraph on page 5, lines 12-21, as follows:

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the soluble IL-1R AcM polypeptide having the amino acid sequence is shown in Figure 1A~~Figure 1~~ [SEQ ID NO:2] or the amino acid sequence encoded by the cDNA clone deposited in a bacterial host as ATCC Deposit Number 97666 on July 25, 1996. The nucleotide sequence determined by sequencing the deposited IL-1R AcM clone, which is shown in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1], contains an open reading frame encoding a polypeptide of 356 amino acid residues, including an initiation codon at positions 303-305, with a leader sequence of about 17 amino acid residues, and a predicted molecular weight of about 42 kDa. The amino acid sequence of the mature IL-1R AcM protein is amino acid residues 18-356 shown in Figures 1A-B~~Figure 1~~ or 1-339 shown in SEQ ID NO:2.

Please amend the paragraph on page 6, lines 20-24, as follows:

Figures 1A-B~~Figure 1~~ shows the nucleotide [SEQ ID NO:1] and deduced amino acid [SEQ ID NO:2] sequences of soluble IL-1R AcM. The protein has a leader sequence of about 17 amino acid residues (underlined) and a deduced molecular weight of about 42 kDa. The predicted amino acid sequence of the mature soluble IL-1R AcM protein is also shown in Figure 1A~~Figure 1~~ [SEQ ID NO:2].

Please amend the paragraph on page 7, lines 3-9, as follows:

Figure 3 shows an analysis of the IL-1R AcM amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown. ~~In the "Antigenic Index - Jameson-Wolf" graph (boxed graph), t~~The amino acid sequence of the IL-1R AcM protein is shown with the amino acids ~~aieds~~ that border each peak from the "Antigenic Index - Jameson-Wolf" plot~~antigenic index plot~~ displayed as underlined characters.

Please amend the paragraph on page 7, lines 11-21, as follows:

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding soluble IL-1R AcM polypeptide, having the amino acid sequence

shown in Figure 1A~~Figure 1~~ [SEQ ID NO:2], which was determined by sequencing a cloned cDNA. The soluble IL-1R AcM protein of the present invention shares sequence homology with mouse interleukin 1 receptor accessory protein (Figure 2) [SEQ ID NO:3]. The nucleotide sequence shown in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1] was obtained by sequencing the HMEEJ22 clone, which was deposited on July 25, 1996 at the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, and given accession number 97666. The deposited clone is inserted in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA).

Please amend the paragraph beginning on page 8, lines 17 through p. 9, line 6, as follows:

Using the information provided herein, such as the nucleotide sequence in Figures 1A-B~~Figure 1~~, a nucleic acid molecule of the present invention encoding a soluble IL-1R AcM polypeptide may be obtained using standard cloning and screening procedures, such as those for cloning cDNAs using mRNA as starting material. Illustrative of the invention, the nucleic acid molecule described in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1] was discovered in a cDNA library derived from human microvascular endothelial cells. The determined nucleotide sequence of the soluble IL-1R AcM cDNA of Figures 1A-B~~Figure 1~~ [SEQ ID NO:1] contains an open reading frame encoding a protein of 356 amino acid residues, with an initiation codon at positions 303-306 of the nucleotide sequence in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1], a predicted leader sequence of about 17 amino acid residues, and a deduced molecular weight of about 42 kDa. The amino acid sequence of the predicted mature soluble IL-1R AcM is amino acid residue 18 to residue 356 shown in Figure 1A~~Figure 1~~ or amino acids 1-339 shown in SEQ ID NO:2. The soluble IL-1R AcM protein shown in Figure 1A~~Figure 1~~ [SEQ ID NO:2] is about 94% similar and 85% identical to mouse interleukin 1 accessory protein (Figure 2A). In addition, the nucleotides 1060 to 1353 of soluble IL-1R AcM protein shown in Figure 1A~~Figure 1~~ [SEQ ID NO:2] is about 99% similar and 98% identical to the first 294 nucleotides partial cDNA isolated from human infant brain by Adams, M.D., *et al., Nature Genet. 4*:373-380 (1993) [SEQ ID NO:4](Figure 2B). The partial cDNA isolated by Adams was 396 nucleotides in length.

Please amend the paragraph on page 11, lines 13-22, as follows:

Isolated nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) with an initiation codon at positions 303-306 of the nucleotide sequence shown in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1]; DNA molecules comprising the coding sequence for the mature soluble IL-1R AcM protein shown in Figure 1A~~Figure 1~~ (last 339 amino acids) [SEQ ID NO:2]; and DNA molecules which comprise a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode the soluble IL-1R AcM protein. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate the degenerate variants described above.

Please amend the paragraph on page 12, lines 3-18, as follows:

In another aspect, the invention provides isolated nucleic acid molecules encoding the soluble IL-1R AcM polypeptide having an amino acid sequence encoded by the cDNA clone contained in the plasmid deposited as ATCC Deposit No. 97666 on July 25, 1996. In a further embodiment, nucleic acid molecules are provided encoding the mature soluble IL-1R AcM polypeptide or the full-length soluble IL-1R AcM polypeptide lacking the N-terminal methionine. The invention also provides an isolated nucleic acid molecule will encode the mature polypeptide encoded by the above-described deposited cDNA clone. The invention further provides an isolated nucleic acid molecule having the nucleotide sequence shown in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1] or the nucleotide sequence of the soluble IL-1R AcM cDNA contained in the above-described deposited clone, or a nucleic acid molecule having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful as probes for gene mapping, by *in situ* hybridization with chromosomes, and for detecting expression of the soluble IL-1R AcM gene in human tissue, for instance, by Northern blot analysis.

Please amend the paragraphs beginning on page 13, line 29 through page 15, line 10, as follows:

Since a soluble IL-1R AcM cDNA clone has been deposited and its determined nucleotide sequence is provided in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1], generating polynucleotides which hybridize to a portion of the soluble IL-1R AcM cDNA molecule

would be routine to the skilled artisan. For example, restriction endonuclease cleavage or shearing by sonication of the soluble IL-1R AcM cDNA clone could easily be used to generate DNA portions of various sizes which are polynucleotides that hybridize to a portion of the soluble IL-1R AcM cDNA molecule. Alternatively, the hybridizing polynucleotides of the present invention could be generated synthetically according to known techniques. Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3' terminal poly(A) tract of the soluble IL-1R AcM cDNA shown in Figure 1B~~Figure 1~~ [SEQ ID NO:1]), or to a complementary stretch of T (or U) resides, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

Preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding epitope-bearing portions of the soluble IL-1R AcM protein. In particular, isolated nucleic acid molecules are provided encoding polypeptides comprising the following amino acid residues in Figure 1A~~Figure 1~~ (SEQ ID NO:2), which the present inventors have determined are antigenic regions of the soluble IL-1R AcM protein:In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a polypeptide comprising amino acid residues from about 6 to about 15 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 57 to about 66 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 70 to about 79 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 106 to about 112 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 115 to about 124 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 129 to about 135 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 158 to about 172 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 180 to about 187 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 207 to about 215 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 231 to about 244 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 247 to about 255 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 268 to about 276 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 285 to about 295 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 303 to about 310 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about 319 to about 330 in

SEQ ID NO:2; and a polypeptide comprising amino acid residues from about 333 to about 339 in SEQ ID NO:2. Methods for generating such epitope-bearing portions of soluble IL-1R AcM are described in detail below.

Please amend the paragraph on page 16, lines 12-23, as follows:

Such variants include those produced by nucleotide substitutions, deletions or additions. The substitutions, deletions or additions may involve one or more nucleotides. The variants may be altered in coding regoins, non-coding regions, or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the soluble IL-1R AcM protein or portions thereof. Also especially preferred in this regard are conservative substitutions. Most highly preferred are nucleic acid molecules encoding the mature protein having the amino acid sequence shown in Figure 1A~~Figure 1~~ [SEQ ID NO:2] or the mature soluble IL-1R AcM amino acid sequence encoded by the deposited cDNA clone.

Please amend the paragraphs beginning on page 17, line 22 through page 19, line 5, as follows:

As a practical matter, whether any particular nucleic acid molecule is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the nucleotide sequence shown in Figures 1A-B~~Figure 1~~ or to the nucleotides sequence of the deposited cDNA clone can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711. Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics 2*: 482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1] or to the nucleic acid sequence of the deposited cDNA, irrespective of whether they encode a polypeptide having soluble IL-1R AcM activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having soluble IL-1R AcM activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having soluble IL-1R AcM activity include, *inter alia,* (1) isolating the soluble IL-1R AcM gene or allelic variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the soluble IL-1R AcM gene, as described in Verma *et al., Human Chromosomes: A Manual of Basic Techniques*, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting soluble IL-1R AcM mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 90%, 95%, 97%, 98% or 99% identical to the nucleic acid sequence shown in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1] or to the nucleic acid sequence of the deposited cDNA which do, in fact, encode a polypeptide having soluble IL-1R AcM protein activity. By "a polypeptide having soluble IL-1R AcM activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of the soluble IL-1R AcM protein of the invention (either the full-length protein or, preferably, the mature protein), as measured in a particular biological assay. Assays of IL-1R AcM protein activity are well-known to those in the art. These assays can be used to measure IL-1R AcM protein activity of partially purified or purified native or recombinant protein. For example, an equilibrium and competitive binding studies using CHO stable cell lines (Greenfeder *et al., J. Biol. Chem. 270: 13757-13765 (1995))* can be performed to detect IL-1R AcM activity.

Please amend the paragraph bridging page 20, line 29 through page 21, line 11, as follows:

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequence

of the deposited cDNA or the nucleic acid sequence shown in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1] will encode a polypeptide "having soluble IL-1R AcM protein activity." In fact, since degenerate variants of these nucleotide sequences all encode the same polypeptide, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having soluble IL-1R AcM protein activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

Please amend the paragraph on page 25, lines 19-28, as follows:

The invention further provides an isolated soluble IL-1R AcM polypeptide having the amino acid sequence encoded by the deposited cDNA, or the amino acid sequence in Figure 1A~~Figure 1~~ [SEQ ID NO:2], or a peptide or polypeptide comprising a portion of the above polypeptides. The terms "peptide" and "oligopeptide" are considered synonymous (as is commonly recognized) and each term can be used interchangeably as the context requires to indicate a chain of at least to amino acids coupled by peptidyl linkages. The word "polypeptide" is used herein for chains containing more than ten amino acid residues. All oligopeptide and polypeptide formulas or sequences herein are written from left to right and in the direction from amino terminus to carboxy terminus.

Please amend the paragraph on page 30, lines 3-15, as follows:

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figure 1A~~Figure 1~~ [SEQ ID NO:2] or to the amino acid sequence encoded by deposited cDNA clone can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full

length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

Please amend the paragraphs beginning on page 47, line 20, through p. 48, line 2, as follows:

The 5' oligonucleotide primer has the sequence 5' GGATCCATGACACTTCTGTGGTGTG 3' (SEQ ID NO:23) containing the underlined BamHI restriction site, followed by 16 nucleotides complementary to bp 1834-1853 of the antisense strand of the IL-1R AcM protein coding sequence set out in Figures 1A-B ~~Figure 1~~ (SEQ ID NO:1).

The 3' primer has the sequence 5' GTCGACTCACTGACCGCATCT 3' (SEQ ID NO:24) containing the underlined SalI restriction site, followed by 15 nucleotides complementary to bp 1056-1071 of the sense strand of the IL-1R AcM protein coding sequence set out in Figures 1A-B~~Figure 1~~ (SEQ ID NO:1), and a stop codon.

Please amend the paragraphs on page 54, lines 17-29, as follows:

The 5′ primer has the sequence 5′GACTGGATCCGCCATCATGACACTTCTGTGGTGTG 3′ (SEQ ID NO:27) containing the underlined BamH1 restriction enzyme site followed by 19 bases of the sequence of IL-1R AcM of Figures 1A-B~~Figure 1~~ (SEQ ID NO:1). Inserted into an expression vector, as described below, the 5′ end of the amplified fragment encoding human IL-1R AcM provides an efficient signal peptide. An efficient signal for initiation of translation in eukaryotic cells, as described by Kozak, M., J. Mol. Biol. 196:947-950 (1987) is appropriately located in the vector portion of the construct.

The 3′ primer has the sequence 5′ GAATTCCTCACTGACCGCATCT 3′ (SEQ ID NO:28) containing the EcoRI restriction followed by nucleotides complementary to the last 15 nucleotides of the IL-1R AcM coding sequence set out in Figures 1A-B~~Figure 1~~ (SEQ ID NO:1), including the stop codon.

Please amend the paragraphs on page 56, lines 6-20, as follows:

The 5' primer has the sequence 5' GACTGGATCCGCCATCATGACACTTCTGTGGTGTG 3' (SEQ ID NO:29) containing the underlined BamHI restriction enzyme site followed by 19 bases (bp 1834-1853) complementary to the antisense strand of the soluble IL-1R AcM protein coding sequence of Figures 1A-B~~Figure 1~~ (SEQ ID NO:1). Inserted into an expression vector, as described below, the 5' end of the amplified fragment encoding soluble IL-1R AcM protein receptor provides an efficient signal peptide. An efficient signal for initiation of translation in eukaryotic cells, as described by Kozak, M., *J. Mol. Biol. 196*:947-950 (1987), may be located, as appropriate, in the vector portion of the construct.

For the full length gene, the 3' primer has the full length sequence 5' GAC TGG TAC CCA TAG AAA TCA TGT GTA TAC C 3' (SEQ ID NO:30), containing the underlined Asp718 restriction followed by 25 nucleotides complementary to bp 2049-2070 of the sense strand of the soluble IL-1R AcM protein set out in Figures 1A-B~~Figure 1~~ [SEQ ID NO:1], and a stop codon.